IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF Art Unit: 1619

GREIL ET AL.

APPLICATION NO: 10/001,544

FILED: OCTOBER 31, 2001

FOR: CRYSTALLINE BETA-LACTAM INTERMEDIATE

DECLARATION UNDER 37 C.F.R. §1.132

I, Johannes Ludescher, make the following declaration in connection with the above-identified patent application.

1. I am a citizen of Austria, residing at Kleinsoell 101, A-6252 Breitenbach, Austria.

2. I am a chemist by training and experience. In 1980 I received the degree of Doctor of Philosophy in chemistry, on the topic of synthesis of ß-lactam antibiotics, from the University of Innsbruck, Austria.

3. From 1981 to 1982, I undertook post-doctorate studies with Dr. I.W. Gensler at Boston University Boston, MA. From 1982 to 1984, I held a post-doctorate position with the Sandoz Research Institute in Vienna, Austria working on the synthesis of ß-lactam antibiotics, in particular carbapenems.

4. In 1984, I joined the Research and Development department of Biochemie GmbH, Kundl, Austria as a research chemist specializing in synthesis and purification of penicillins and cephalosporins. I am presently the head of Basic Chemical Development at Sandoz GmbH, which is the new name of former Biochemie GmbH.

5. I have authored a paper on the Chemistry of Penicillin Diazoketones, Part II; Betalactam to Betalacton: Heterocycles 26.4.p.885 (1987). In addition, I am an inventor of at least 35 U.S. patents, and 18 U.S. patent applications which are currently pending.

6. I am an inventor of the above-identified patent application. I have read and understood the patent application and I am familiar with the invention described and claimed therein. In addition, I have reviewed JP 3-031286 and JP 60-004189 which I understand were cited as prior art against the claims of the above-identified application.

7. Under my direction, experiments were carried out concerning the preparation of N-formyl-cefpodoxime proxetil and its crystalline or amorphous status. The experiments and their results are set forth below.

8. Description of Experiments:

Experiment I

Preparation of N-formyl-cefpodoxime proxetil according to the teachings of JP 3-031286 and JP 60-004189. (Laboratory batch WS 94/58).

A) Fine needles of Isomer A of 1-(isopropyloxycarbonyloxy)ethyl-7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem 4 carboxylate (diastreomeric purity 99.4 % Isomer A) were obtained by acylating the isomer A of 1-(isopropyloxycarbonyloxy)ethyl)-7-amino-3-methoxymethyl-3-cephem-4-carboxylate with 2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid using N,N-dimethylformamide/$POCl_3$ as activating agent and $NaHCO_3$ as a base in ethylacetate.

B) Fine needles of Isomer B of 1-(isopropyloxycarbonyloxy)ethyl-7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem 4 carboxylate (diastereomeric purity : 99% Isomer B), were obtained by acylating the isomer B of 1-(isopropyloxycarbonyloxy)ethyl)-7-amino-3-methoxymethyl-3-cephem-4-carboxylate with 2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyiminoacetic acid using N,N-dimethylformamide/$POCl_3$ as activating agent and $NaHCO_3$ as a base in ethylacetate.

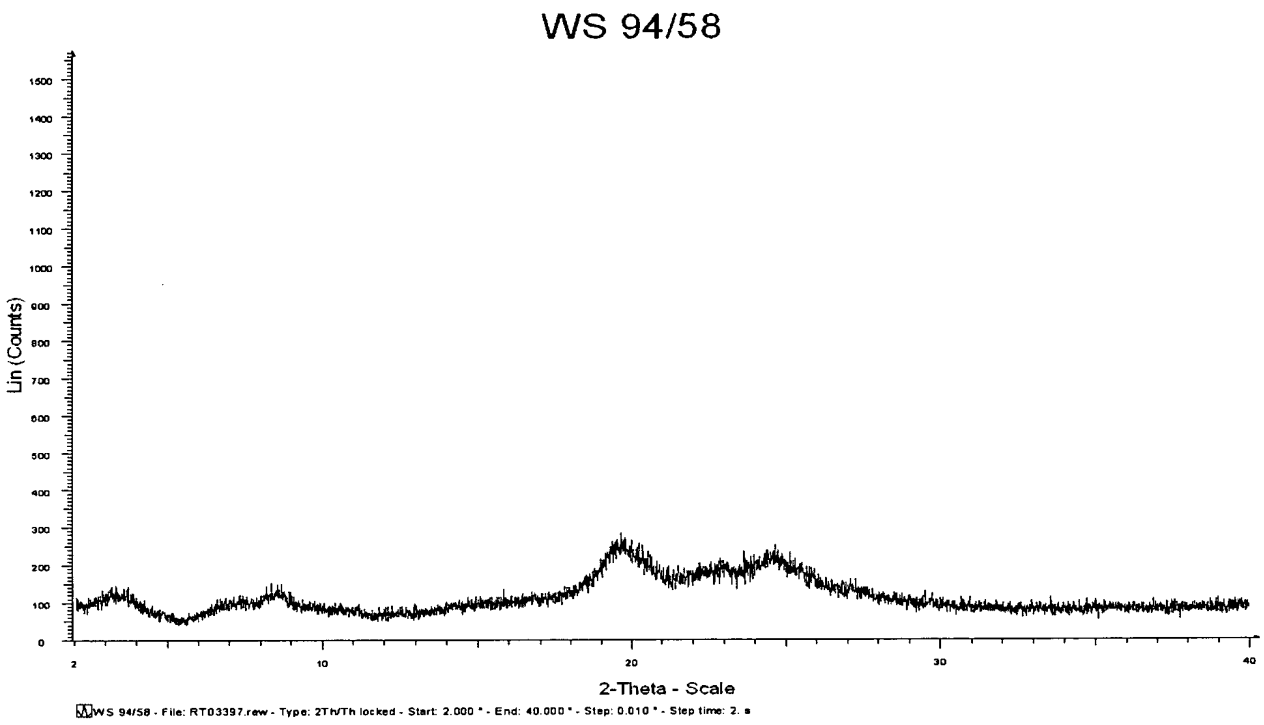
C) 1.0 g of isomer A of 1-(isopropyloxycarbonyloxy)ethyl-7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem 4 carboxylate as obtained from above described step A) was dissolved in 30 ml of ethylacetate.

D) 1.0 g of isomer B of 1-(isopropyloxycarbonyloxy)ethyl-7-[2-(2-formylaminothiazol-4-yl)-(Z)-2-methoxyimino-acetamido]-3-methoxymethyl-3-cephem 4 carboxylate as obtained from above described step B) was suspended in 40 ml of ethylacetate. No solution was obtained.

E) The solution obtained from step C) and the suspension obtained from step D) were combined, 20 ml of ethylacetate were added and a slightly turbid solution was obtained. This solution was filtered and the filtrate was concentrated on a rotary evaporator (reduced pressure approximately 100 mbar, bath temperature 35°C) *in vacuo*. A colourless solid was obtained. 20 ml of diisopropylether were added to the solid, lumps were broken with a spatula and with aid of an ultrasonic bath. The solid was isolated by filtration and dried at room temperature for 5 hours *in vacuo*.
Yield : 1.77 g

F) An X-ray powder diffraction pattern of the N-formyl-cefpodoxime proxetil obtained from step E) was determined in an X-ray powder diffractometer D-8 (AXS-BRUKER, theta-theta-goniometer, sample changer, target: copper, $K\alpha1+K\alpha2$ $\lambda=1.5406$Å, parallel beam optics with receiving soller-slit 0.07mm, scintillation counter, standard sample holders) applying the following measurement conditions: 40kV, 40mA, 2-40° $\theta/2\theta$, steps 0.01, step time 2 sec. The X-ray powder diffraction pattern is shown in Figure 1.

Fig. 1



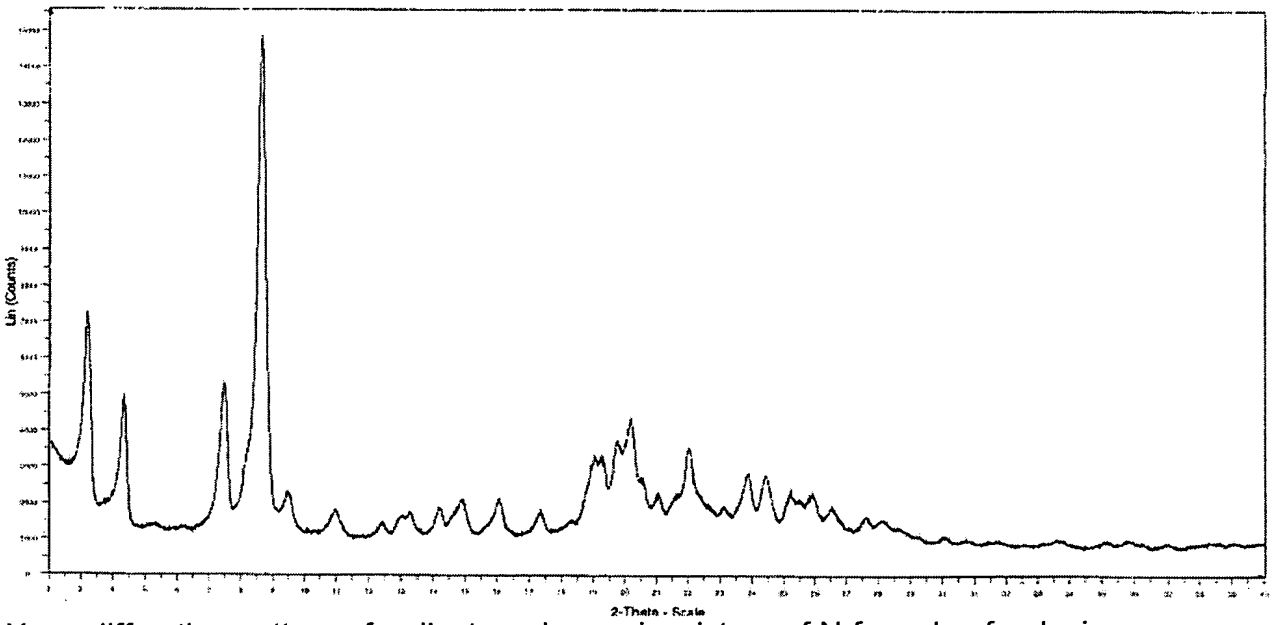
X-ray powder diffraction pattern of N-formyl-cefpodoxime proxetil obtained according to **JP 3-031286 and JP 60-004189.**

Experiment II

Preparation of N-formyl-cefpodoxime proxetil according to Example 2a) of the above-identified patent application.

a) 3 g of amorphous N-formyl cefpodoxime proxetil with a diastereomeric ratio B/(A+B) of 0.51 and a HPLC purity of 97% are dissolved in a mixture of 6 ml of DMF and 15 ml of acetonitrile. At room temperature 20 ml of water are added . Seeds are added and a suspension of fine crystals is obtained. Further 30 ml of water are added slowly within 30 min and the suspension is isolated by filtration after further 15 min. The crystals are dried *in vacuo* at 40°C overnight.
Yield: 2.63 g
b) An X-ray powder diffraction pattern of the N-formyl-cefpodoxime proxetil obtained from step a) was determined in an X-ray powder diffractometer D-8 (AXS-BRUKER, theta-theta-goniometer, sample changer, target: copper, Kα1+Kα2 λ=1.5406Å, parallel beam optics with receiving soller-slit 0.07mm, scintillation counter, standard sample holders) applying the following measurement conditions: 40kV, 40mA, 2-40° θ/2θ, steps 0.01, step time 2 sec. The X-ray powder diffraction pattern is shown in Figure 2.

Fig. 2



X-ray diffraction pattern of a diastereoisomeric mixture of N-formyl-cefpodoxime proxetil prepared according to Ex. 2a of the above-identified application.

9. Conclusion:
   It is clear that the X-ray powder diffraction pattern of N-formyl-cefpodoxime proxetil as shown in Fig. 1 does not have any distinct peaks. Thus, the N-formyl-cefpodoxime proxetil that was described as the starting material in Example 1 of JP-3-31286 which was prepared according to JP 60-004189 is noncrystalline or amorphous. In contrast, the X-ray powder diffraction pattern of Fig. 2 shows clear distinct peaks indicating that the N-formyl-cefpodoxime proxetil prepared according to Example 2a) of the above-identified application is crystalline.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Kundl, November 25, 2004

Johannes Ludescher, Ph.D.